Please cancel claims 35, 37, 43, 45, 49, 50, 51, 52, 53, 54, 55, 56, 57 and 58 without prejudice.

REMARKS

Claims 12, 15, 16, 21, 23, 24, 26-33, 35, 37, 43-45 and 49-59 are pending in the instant application. Claims 12, 15, 16, 21, 23, 24, 26-33, 35, 37, 43-45 and 49-59 have been rejected. Claims 12 and 26 have been amended. Claims 35, 37, 43, 45, 49, 50, 51, 52, 53, 54, 55, 56, 57 and 58 have been canceled. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims 35, 37, 43 and 45-49 under 35 U.S.C. § 112, first paragraph

The rejection of claims 35, 37, 43 and 45-59 under 35 U.S.C. § 112, first paragraph, has been maintained.

With respect to claims 35, 37, 43 and 45-58 drawn to methods for treating a neurological or neurodegenerative disease, the Examiner suggests that the specification does not disclose any specific neuronal disorder which has been subjected to the claim designated treatment regimen. Further, the Examiner suggests that the state of the art at the time of filing teaches that neuronal transplantation techniques and *in vivo* therapeutic effectiveness

had not been established such that utilizing cells to treat neuronal disorders was routine or predictable.

Applicants respectfully disagree with the Examiner's characterization of the art as unpredictable and the requirement that working examples be provided to enable claims drawn to cell and gene therapy strategies for treating neuronal disorders. However, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 35, 37, 43 and 45-58 without prejudice.

With respect to claim 59, drawn to a method of isolating a pure population of mouse or human CNS neuron-restricted precursor cells via a sample of mouse or human embryonic stem cells, the Examiner suggests that the specification is not enabling for isolating a pure population of human CNS neuron-restricted precursor cells using human embryonic stems cells as starting material. The Examiner suggests that for a population of cells to be defined as embryonic stem cells, establishment that the embryonic stem cells retain their totipotential capacity and are able to generate cells of all lineages, including germline, after being introduced into a host blastocyte, is necessary. The Examiner suggests that neither the specification or the prior art references by Thompson et al. demonstrate this.

Applicants respectfully traverse this rejection.

At the outset, it is respectfully pointed out that Applicants are not attempting to define human ES cells in the instant invention. Instead, Applicants merely cited Thompson as evidence of the fact that human ES cells are known in the art and therefore, like mouse ES cells, can serve as a starting material in the method of the present invention.

Further, Applicants respectfully disagree with the Examiner's suggestion of requirements for what must be established to define a population of cells as embryonic stem cells. Legal and ethical considerations prevent using human ES cells to generate embryos and demonstrate germline transmission. Hence, other criteria have been used by those of skill in the art to define human ES cells. These include: expression of ES cell specific markers such as UTF-1, Oct-3, and FGF4 expression; the ability to generate ectoderm, endoderm and mesodermal derivatives in culture; the ability to form teratocarcinomas; and levels of telomerase activity. Based on these parameters, the vast majority of scientists have acknowledged that Thompson et al. have derived human ES cells. Thus, the Examiner's basis for questioning the enablement of claim 59 is flawed as those of skill in the art clearly accept Thompson et al. as providing human ES cells. Accordingly, contrary to the

Examiner's suggestion, one of skill in the art could clearly make and use the instant invention commensurate in scope with claim 59. Therefore, claim 59 meets the requirements of 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

II. Rejection of Claims 12, 15, 16 and 26 under 35 U.S.C. § 112, second paragraph

Claims 12, 15, 16 and 26 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that claim 12 is vague and indefinite for the phrase "NEP medium configured for inducing said cells to begin differentiating" because it is unclear if the cells are incubated in NEP medium, as defined in the specification, or if the NEP medium is altered such that it induces the cells to begin differentiating. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 12 to delete this phrase and to add a step clarifying the conditions in which the NEP cells are induced to differentiate. Support for this amendment can be found in the specification at page 37, lines 8-9.

The Examiner also suggests that the phrase "wherein said neuron-restricted precursor cells require FGF" is vague as it is unclear if the cells require FGF in step (b) of the method to induce differentiation, or if FGF is required in step (d) for supporting adherent growth of the purified subpopulations. Accordingly, Applicants have amended the claims to clarify that FGF is required to support adherent growth. Support for this amendment can be found in the specification at page 31, lines 18-20, page 35, lines 6-11, and page 37, lines 8-9.

Finally, the Examiner suggests that it is unclear what culture conditions are required which support adherent cell growth and which result in the differentiation of the cells into CNS neuronal cells but not CNS glial cells. Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended the claims to clarify conditions which promote adherent growth, promote differentiation into neurons and do not promote proliferation and/or differentiation into glial cells. Support for these amendments can be found in throughout the specification. For example, see page 31, lines 18-21, and page 33, line 19, through page 34, line 9.

Withdrawal of these rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested in light of these amendments.

III. Rejection of Claims 21, 23, 26 and 27 under 35 U.S.C. § 102(b)

Claims 21, 23, 26 and 27 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Blass-Kampmann et al. (J. Neuroscience Research 37:359-373, 1994). Arguments presented in the previous response regarding the different characteristics of the cells of the instant invention versus those of Blass-Kampmann et al. were considered unpersuasive because the method steps recited in the claims which produce the cells of the instant invention are suggested by the Examiner to be undistinguishable over prior art method steps. Further, the Examiner suggests that the limitation "wherein said neuron-restricted precursor cells require FGF and differentiate into CNS neuronal cells but not into glial cells" would be inherent to the cell population produced by the method of the present invention as well as the prior art method.

Accordingly, in an earnest effort to advance the prosecution of this case, and in accordance with the Examiner's suggestion, Applicants have amended the method claims to recite specific culture conditions which clearly distinguish the present invention from the teachings of Blass-Kampmann et al. Specifically, claims 12, 21, 26 (which depends from claim 12) and 27 (which depends from claim 26) have been amended to clarify that FGF containing media

was used to support adherent growth, that retinoic acid containing medium promotes differentiation to neurons, and that astrocyte-promoting medium containing FGF and 10% fetal calf serum fails to promote proliferation or differentiation. Neither culture in FGF nor retinoic acid is taught in Blass-Kampmann et al. Instead, in the method taught by Blass-Kampmann, the cells were cultured in modified Eagle-Dulbecco medium supplemented with 10% FCS or F14 medium supplemented with 10%, culture conditions now explicitly claimed to neither promote proliferation nor differentiation in the instant invention. Further, Applicants have added a step to claim 12 to clarify that the multipotent CNS stem cells are replated on laminin in the absence of chick embryo extract to induce cell differentiation prior to purifying from the differentiating cells the subpopulation of cells expressing embryonic neural cell adhesion molecules. This step is not taught in the method of Blass-Kampmann et al.

Further, with respect to claims 21 and 27, it is respectfully pointed out that the starting material for the cells is different. The cells of Blass-Kampmann et al. were isolated from fetal brain tissue. In contrast, claims 21 and 27 are drawn to a method and cells produced via a method wherein the cells are isolated from spinal cord tissue from a rodent or human embryo at a stage of

embryonic development after closure of the neural tube but prior to differentiation of glial and neuronal cells in the neural tube.

MPEP § 2131 is quite clear; to anticipate a claim the reference must teach every element of the claim. Since Blass-Kampmann et al. does not teach the culture conditions used to produce the cells as now set forth in the claims, nor all the steps of the claimed methods, nor the same starting material, this reference cannot anticipate the claims as amended.

Withdrawal of this rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

IV. Rejection of Claims 12, 15, 16, 24, 28-33 and 44 under 35 U.S.C. § 103(a)

Claims 12, 15, 16, 24, 38-33 and 44 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Blass-Kampmann et al. (J. Neuroscience Research 37:359-373, 1994) taken with Boss et al. (U.S. Patent 5,411,883, 1995), Weiss et al. (WO/93/01275, 1993), Johe et al. (U.S. Patent 5,753,506, 1998), Rao et al. (26th Annual Meeting of the Society for Neuroscience, 22:527, Abstract 215.12, 1996) and Lee et al. (U.S. Patent 5,175,103, 1992). The Examiner has suggested that Applicants amend the method claims to distinguish the initial and final cell populations of the method, to define the incubation protocols, and to further define the final

cell product obtained as to its morphologic and phenotypic characteristics to overcome the prior art of record.

Accordingly, in an earnest effort to advance the prosecution of this case, and in accordance with the Examiner's suggestion, Applicants have amended the claims to define the incubation protocols, and more particularly the culture media used, and to further define the final cell product obtained as to its phenotypic characteristics, namely the ability to differentiate into neurons upon replacement of adherent growth supporting medium with retinoic acid containing medium and failure to proliferate or differentiate in astrocyte-promoting medium containing FGF and 10% fetal calf serum. Neither a method with the specified conditions nor cells with the claimed phenotypic characteristics are taught or suggested by the combination of prior art references.

The teachings of Blass-Kampmann et al. and differences between this reference and the present invention as now claimed have been discussed in detail in Section III, *supra*.

The secondary references cited in this rejection fail to remedy the deficiencies in the primary reference.

Boss et al. is cited by the Examiner as disclosing that selections of specific neuronal cell type can be performed using FACS, and magnetic bead antibody sorting and that neuron progenitor

cells can be induced to differentiate in vitro by adding a differentiation agent to the culture medium. However, like Blass-Kampmann et al. this reference also teaches different culture medium and method steps to those claimed in the instant invention. For example, at column 7, lines 59-68, Boss et al. teaches that the initial culture medium can be a basal medium supplemented with serum, hormones, growth factors and trace elements. In contrast, as set forth specifically in the amended claims, culture in 10% fetal calf serum does not promote proliferation or differentiation of the cells of the instant invention. As another example, the differentiating agents taught by Boss et al. at col. 13, lines 43-46, namely sodium butyrate, butyric acid, cyclic adenosine monophosphate derivatives, phosphodiesterase inhibitors, adenylate cyclase activators and prostaglandins are different to differentiating conditions claimed in the instant invention.

Johe et al. is cited by the Examiner as disclosing dissociating cells from various regions of embryonic brain and culturing the cells in the presence of either EGF or bFGF to allow proliferation of the cells, and that removing the mitotic agent resulted in differentiation of the cells. However, this reference also discloses different culture conditions and steps to those claimed in the instant invention. For example, at col. 7, line 66,

through col. 8, line 5, it is taught that differentiation may be directed by adding a second growth factor, namely platelet-derived growth factor, ciliary neurotropic factor, leukemia inhibitory factor or thyroid hormone, iodothyromine.

As acknowledged by the Examiner, Weiss et al. disclose methods of differentiating cells by including bFGF. Thus, the method of Weiss et al. is also different from that claimed.

Rao et al. discloses a method for obtaining multipotent stem cells. No method steps or specific conditions for obtaining the neuronal-restricted precursor cells as claimed are either taught or suggested in this Abstract.

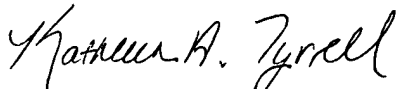
Finally, Lee et al. is suggested by the Examiner to disclose that NT2 cells can be differentiated into greater than 95% pure cultures of neuronal cells when cultured in the presence of retinoic acid and that the neuronal cells can be maintained in a post-mitotic state after withdrawal of mitotic inhibitors. NT2 cells, however, are NTera 2/cl.D1 cells from a human teratocarcinoma cell line. Accordingly, this reference teaches a completely different starting material to that used in the instant claimed invention. Thus, the teachings of Lee et al. are not predictive for the methods and cells of the instant invention.

To render an invention obvious, the prior art when combined must teach or suggest all the limitations of the claimed invention. See MPEP § 2143. Since the prior art references, either alone or in combination, fail to teach or suggest methods or cells produced by methods with all the steps and culture conditions of the claims as amended, they cannot render obvious these claims. Withdrawal of this rejection under 35 U.S.C. § 103(a) is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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